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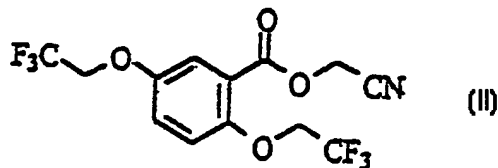
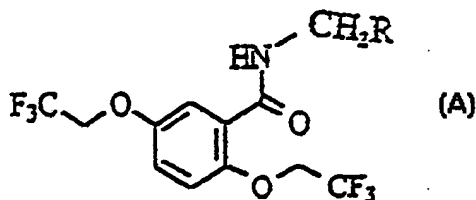
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 213/40, 211/26, C07C 255/14, C07B 43/06</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/02498 (43) International Publication Date: 21 January 1999 (21.01.99)</p>
<p>(21) International Application Number: PCT/IL98/00315 (22) International Filing Date: 7 July 1998 (07.07.98) (30) Priority Data: 121288 11 July 1997 (11.07.97) IL (71) Applicant (for all designated States except US): FINETECH LTD. [IL/IL]; Technion City, P.O. Box 3557, 31032 Haifa (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): GUTMAN, Arie, L. [IL/IL]; Kroch Street 2, 34752 Haifa (IL). NISNEVICH, Genady [IL/IL]; Zahal Street 10/24, 20306 Nesher (IL). SHKOLNIK, Eleonora [IL/IL]; Hasavion Street 8/1, 20306 Nesher (IL). ZALTZMAN, Igor [IL/IL]; Hillel Street 41, 33071 Haifa (IL). (74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	

(54) Title: PROCESS AND A NOVEL INTERMEDIATE FOR THE PREPARATION OF FLECAINIDE

(57) Abstract

The present invention provides a process for the preparation of a compound of formula (A) wherein R is a 2-piperidyl or 2-pyridyl radical, and pharmaceutically acceptable salts thereof, which process comprises the steps of: a) reacting 2,5 bis (2,2,2-trifluoroethoxy) benzoic acid or a salt thereof, with a haloacetonitrile of the formula XCH_2CN , where X is Cl, Br or I, if necessary in the presence of an inorganic or organic base, to form the cyanomethyl ester of formula (II); b) reacting the ester of formula (II) with an amine of the formula RCH_2NH_2 , where R is as defined above and, if desired; c) converting the compound of the formula (A) to a pharmaceutically acceptable salt thereof.



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PROCESS AND A NOVEL INTERMEDIATE FOR THE PREPARATION OF FLECAINIDE

FIELD OF THE INVENTION

This invention relates to a novel process for the preparation of Flecaïnide and a precursor thereof, to a novel intermediate used in this process and its preparation.

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BACKGROUND OF THE INVENTION

Flecaïnide (2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide is an effective antiarrhythmic drug that acts on the cell membrane to reduce fast inward depolarization current.

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One prior art method for preparing Flecaïnide, disclosed inter alia, in British Patent Application No 2,045,760 A, starts from 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid. This starting material is prepared by a multi-stage process, comprising the conversion of 1,4-dibromobenzene or hydroquinone to 1,4-bis(2,2,2-trifluoroethoxy)benzene, which is acetylated to form 2,5-bis(2,2,2-trifluoroethoxy)acetophenone. The acetophenone is then oxidized to form the corresponding benzoic acid derivative, which is then converted to its acid chloride and reacted either with 2-(aminomethyl)piperidine to form the Flecaïnide product in one step or with 2-(aminomethyl)pyridine, followed by catalytic hydrogenation of the pyridine ring, to form the Flecaïnide product in two steps.

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The one step process has a serious disadvantage in that the acid chloride reacts non-selectively with both nitrogen atoms of the 2-(aminomethyl) piperidine, resulting in a mixture of the two acylated isomers. This is the main reason why the two-step process via the pyridine intermediate is commercially preferred. A further disadvantage is due to the fact that the acid chloride intermediate disclosed in GB 2,045,760A is a

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liquid which can not be stored for long periods of time but must be used immediately after it is prepared.

OBJECTS OF THE INVENTION

5 It is an object of this invention to provide a novel process for the preparation of Flecainide and its pharmaceutically acceptable salts, which is free of the above-mentioned disadvantages, starting with commercially available halobenzoic acids and involving the use of simple reagents and low cost solvents, to afford high overall yield of the Flecainide product.

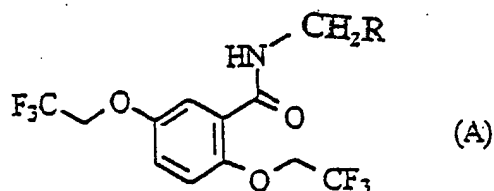
10 It is a further object of this invention to provide a novel reactive intermediate, i.e. the cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, which is capable of reacting selectively with the primary amino group of 2-(aminomethyl)piperidine, so as to form the Flecainide product in high yield and free of the above mentioned isomeric by-product.

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SUMMARY OF THE INVENTION

The above objects are achieved in accordance with the present invention which, in one aspect thereof, provides a process for preparing a compound of formula (A):

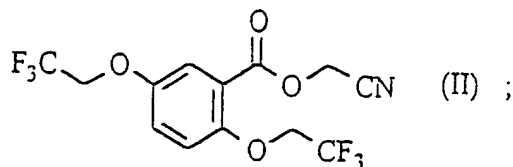
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wherein R is a 2-piperidyl or 2-pyridyl radical, and pharmaceutically acceptable salts thereof, which process comprises the steps of:

a) reacting 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid or a salt thereof, with a haloacetonitrile of the formula XCH_2CN , where X is Cl, Br or I, if necessary in the presence of an inorganic or organic base, to form
30 the cyanomethyl ester of the formula (II):



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b) reacting the ester of the formula (II) with an amine of the formula RCH_2NH_2 , where R is as defined above and, if desired,

10 c) converting the compound of the formula (A) to a pharmaceutically acceptable salt thereof.

In accordance with another aspect of this invention, there is provided the novel cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)-benzoic acid having the formula (II) above. As contrasted to the liquid acid
 15 chloride intermediate disclosed in GB 2,045,760A, the novel intermediate of the present invention is a stable, solid compound, obtainable in high yield, which can be easily purified by crystallisation and stored for long periods of time.

20 DETAILED DESCRIPTION OF THE INVENTION

It was shown by Schwyzer et al. (Helvetica Chimica Acta, 1955, v. 38, 69; 80; 83) that the carboxylic group of aliphatic amino acids, activated by their conversion to their cyanomethyl esters, react selectively with primary amino groups. The present invention is based on the the
 25 unexpected finding that this type of activation may be used with aromatic carboxylic acids, specifically 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid.

Accordingly, the cyanomethyl ester (II) is prepared in high yield, starting with 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid which is reacted with a haloacetonitrile of the formula XCH_2CN wherein X is Cl, Br or I, preferably Cl, in the presence of an inorganic or organic base. Alternatively,
 30 the ester (II) can be prepared by reacting a salt of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid with a haloacetonitrile.

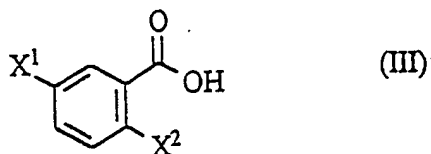
Suitable organic bases for use in the above process are primarily tertiary amines, e.g. triethylamine, diisopropylethylamine, ethylpiperidine and the like, preferably triethylamine. Inorganic bases which may also be used are, e.g., alkali metal or alkaline earth metal carbonates or bicarbonates.

5 In the second step of the process, the cyanomethyl ester (II) is reacted with an amine of the formula RCH_2NH_2 , where R is as defined above, optionally in a suitable, inert solvent. Thus, the reaction may be carried out by mixing together 2-(aminomethyl)piperidine with the ester (II) in a solvent such as 1,2-dimethoxyethane or ethyl acetate, to yield
10 Flecainide (I) in a high yield.

The optional conversion of Flecainide into a pharmaceutically acceptable salt such as the acetate salt, is carried out by conventional methods.

The starting material 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid
15 is preferably prepared by the process described in co-pending Israel Application No. 120715. Accordingly, this benzoic acid derivative is prepared by contacting a halobenzoic acid of the formula (III):

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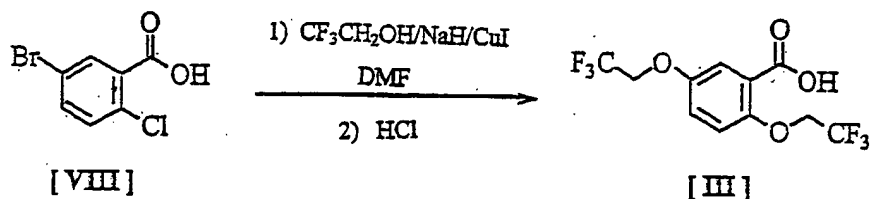
or a salt thereof, wherein X^1 is selected from Br or I, and X^2 is selected
25 from Cl, Br or I, or one of X^1 and X^2 may also be CF_3CH_2O- , with 2,2,2-trifluoroethanol in the presence of a strong base and copper iodide and/or copper bromide, in an aprotic solvent. Suitable solvents are dipolar aprotic solvents or N-containing heterocycles or their mixtures, such as N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, N,N-dimethylacet-
30 amide, DMSO, pyridine, picolines, lutidines, collidines, methylethylpyridine (MEP), quinoline and substituted quinolines. As the strong base there may be used Na, NaH, $NaNH_2$, Na- and K-alcoholates, NaOH, KOH and the

like, most preferably NaH. For example, 5-bromo-2-chlorobenzoic acid is reacted while heating, with 2,2,2-trifluoroethanol and a strong base, e.g. sodium hydride in a dipolar aprotic solvent, e.g. N,N-dimethylformamide, in the presence of copper iodide.

5 The present invention will be described in more detail with the aid of the following non-limiting examples.

EXAMPLE 1

Synthesis of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid



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A 1 L round-bottomed flask equipped with a magnetic stirrer, a thermometer pocket, dropping funnel and a reflux condenser, was charged with 51.0 g of a 60 % strength suspension of sodium hydride in mineral oil (equivalent to a total of 30.6 g (1.28 mole) of pure NaH) and 570 mL of anhydrous N,N-dimethylformamide. The mixture was cooled to room temperature in an ice-water bath and 189.5 g (1.90 mole) of anhydrous 2,2,2-trifluoroethanol were added dropwise during 40 minutes.

The mixture was cooled to room temperature and 24.8 g (0.13 mole) of anhydrous copper iodide and 59.5 g (0.25 mole) of 5-bromo-2-chlorobenzoic acid were added. The black reaction mixture was heated to about 110 - 115 °C and kept at this temperature for 2 hours.

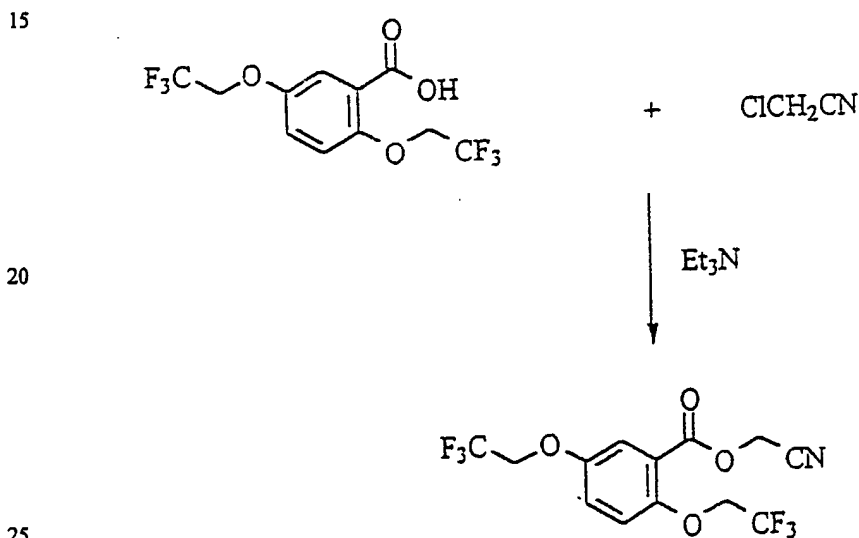
The reaction mixture was cooled to room temperature and poured into a mixture of crushed ice (3 kg) and conc. hydrochloric acid (0.78 L). The mixture was vigorously stirred for 1 hour, the black precipitate was filtered off and washed at once with 200 mL of water. The obtained solid was suspended at room temperature in 1 L of 5 % aqueous KOH under vigorous stirring for 15

min, followed by filtration through a Celite modified filter and washing with 100 mL of 5 % aqueous KOH.

The transparent clear alkaline solution was thrice extracted with 150 mL of dichloromethane. The alkaline solution was added dropwise under vigorous stirring to mixture of 0.6 kg of ice and 0.2 L of conc. hydrochloric acid, at a temperature not higher than 0°C and a pH 1. The mixture was stirred for 0.5 hours at these conditions. The obtained precipitate was filtered off, washed with water, collected and dried under vacuum to a constant weight. Yield: 64.7 g (81.4%) of crude 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, m.p. 116 -118°C. After recrystallisation from an ethanol/water system, a product with m.p. 120-121°C was obtained.

EXAMPLE 2

Synthesis of cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid



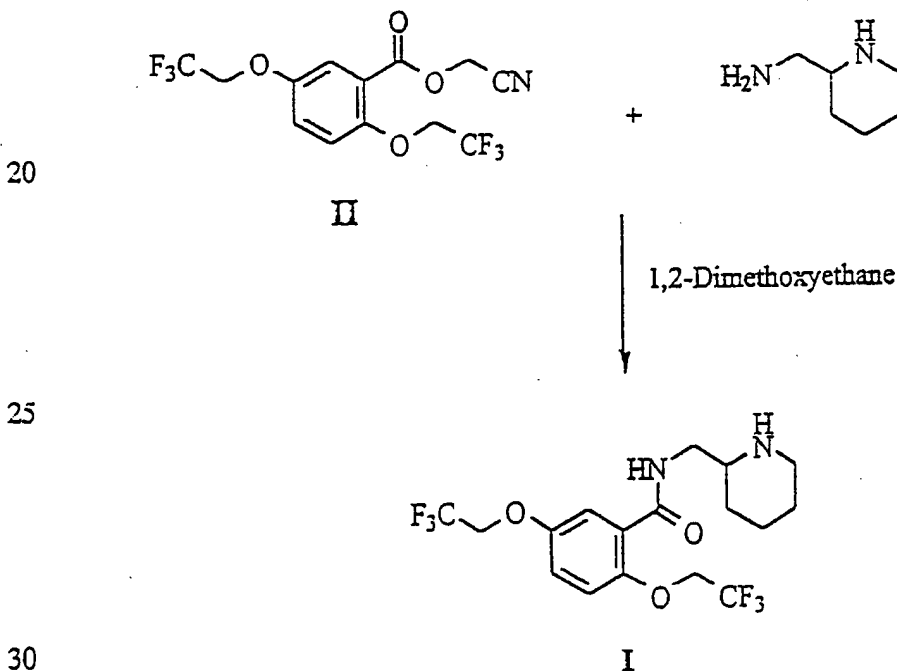
II

A 1 L two-neck round-bottomed flask equipped with a heating mantle, a magnetic stirrer and a reflux condenser was charged under argon with a mixture of 62.8g (197.4 mmole) of 2,5-bis(2,2,2-trifluoroethoxy)-

xy)benzoic acid, 22.4g (296.1 mmole) of chloroacetonitrile and 29.9g (296.1 mmole) of triethylamine in 250 mL ethyl acetate (EtOAc). The obtained mixture was refluxed for 3 hours. After cooling to 10°C, the mixture was filtered through a column containing 50g of silica gel to remove the formed triethylammonium chloride. The filtrate was evaporated in vacuo and the product was dried under high vacuum for 1 hour at 50°C. The resulting colourless solidified oil was stirred with 200 mL of cold hexane to obtain white crystals. The crystals were filtered off, washed with cold hexane and dried at reduced pressure to give 60.0 g (85% yield) of cyanomethyl ester (II), having a purity of 99.5 % (GC), m.p. 50–51°C, one spot on TLC. ¹H NMR (CDCl₃) δ 4.37 (4H, m); 4.93 (2H, s); 7.00 (1H, d); 7.17 (1H, dd); 7.44 (1H, d); HRMS: M⁺ 357.0433, C₁₃H₉NO₄F₆.

EXAMPLE 3

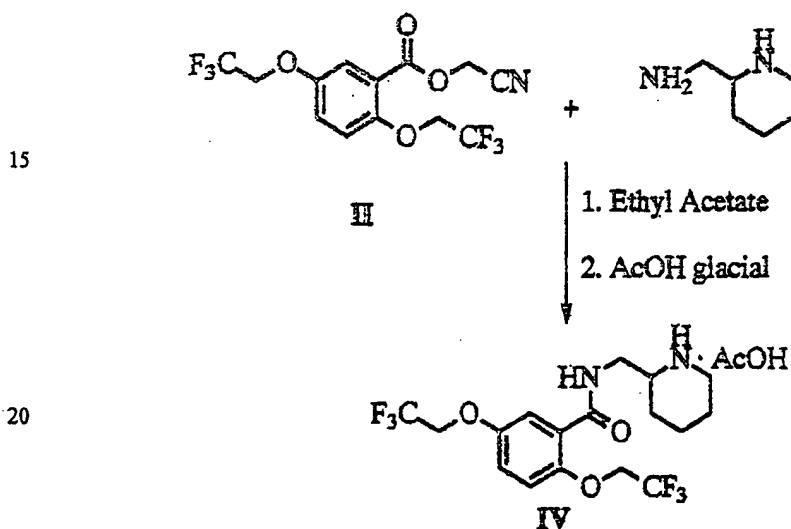
Synthesis of Flecainide (I) from the cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (II) and 2-(aminomethyl)piperidine



A mixture of compound (II) (2.1 g, 5.9 mmole) and 2-(aminomethyl)piperidine (0.8 g, 7 mmole) in 1,2-dimethoxyethane (10 mL) was charged

under argon into a 50 mL round-bottomed flask equipped with a magnetic stirrer. After stirring for 2.5 hours at room temperature, additional 2-(aminomethyl)piperidine (0.5 g, 4.7 mmole) was added. The mixture was stirred for additional 24 hours at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in 10 mL methylene chloride. The obtained solution was extracted with water and the aqueous layer was extracted with additional 5 mL of methylene chloride. The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to give 1.9 g (77.6 % yield) of white crystals of Flecaïnide (I), purity 99.1 % (GC).

Example 4: SYNTHESIS OF FLECAÏNIDE ACETATE (IV)



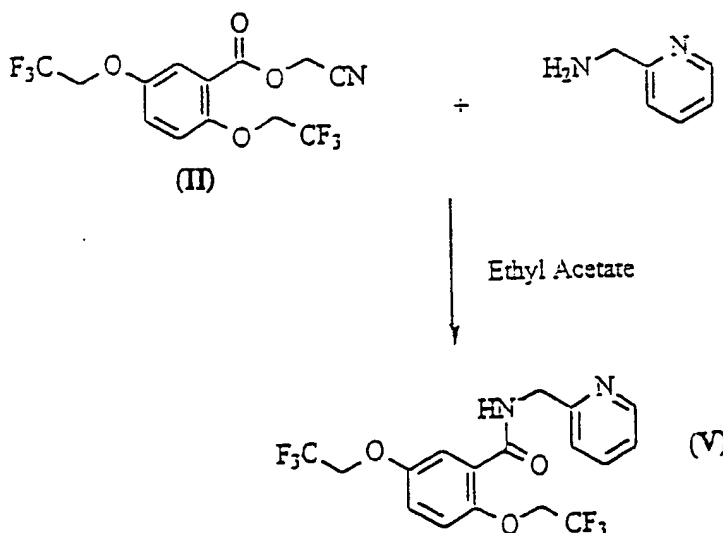
A mixture of compound (II) (95.0g, 0.27 mole) and 2-(aminomethyl)piperidine (35.4 g, 0.31 mole) in 450 mL ethyl acetate (max water content: 0.05%) was charged under argon into a 1 L round-bottomed flask equipped with a dropping funnel and magnetic stirrer. After stirring for 2 hours at room temperature, the additional amount (24.2g, 0.21 mole) of 2-(aminomethyl)piperidine was added and the mixture was stirred for an additional period of 12 hours at room temperature.

The solvent was evaporated under reduced pressure. The residue was dissolved in 250 mL of dichloromethane. The obtained solution was treated with water (3X 50 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure.

The residue was dissolved in boiling ethyl acetate (800 mL), and 30g (0.5 mole) of glacial acetic acid was added dropwise to the obtained solution. The mixture was stirred under reflux for an additional 10 minutes and allowed to cool to room temperature overnight followed by cooling into an ice bath for 4 hours. The crystalline product was filtered off, washed with cooled to 0 ° C ethyl acetate (2 X 100 mL) and dried at 50 ° C under reduced pressure, to obtain 103.0 g (82% from theoretical yield) of Flecainide acetate, m.p. 147-148 ° C.

EXAMPLE 5

Synthesis of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)-benzamide (V)



To a solution of 8.93 g (2.5 mmole) of compound (II) in 80 mL of ethyl acetate under argon, 2-(aminomethyl)pyridine (3.2 g, 3.0 mmole) were added with stirring and the mixture was refluxed for 4 hours. An additional 1 g of 2-(aminomethyl)pyridine was added and the mixture was refluxed for two more hours. The ethyl acetate was evaporated under reduced pressure and the residue was passed through a 12 cm column

containing silica gel with a mixture of methylene chloride : hexane (1:1) as eluent. The column was washed with methylene chloride and the combined solutions were evaporated under reduced pressure. The residue was crystallised from CH_2Cl_2 : hexane (1 : 2) to give 7 g (69 % yield) of
5 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)benzamide (V) m.p. 104-106°C, purity 99.8 % (GC).

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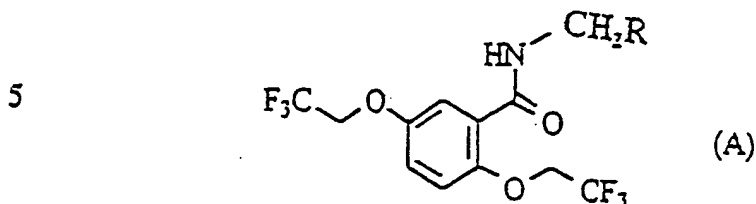
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CLAIMS

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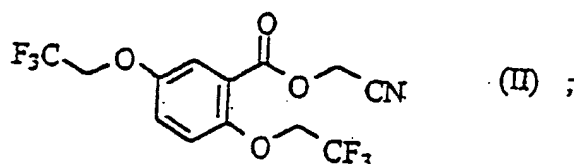
1. A process for the preparation of a compound of formula (A):



wherein R is a 2-piperidyl or 2-pyridyl radical, and pharmaceutically acceptable salts thereof, which process comprises the steps of:

a) reacting 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid or a salt thereof, with a haloacetonitrile of the formula XCH_2CN , where X is Cl, Br or I, if necessary in the presence of an inorganic or organic base, to form the cyanomethyl ester of the formula (II):

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b) reacting the ester of the formula (II) with an amine of the formula RCH_2NH_2 , where R is as defined above and, if desired,

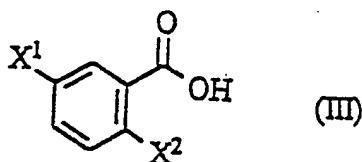
c) converting the compound of the formula (A) to a pharmaceutically acceptable salt thereof.

- 25 2. A process according to claim 1, wherein the reactions in steps a) and/or b) and/or c) are carried out in a suitable inert solvent.

3. A process according to claim 2, wherein ethyl acetate is used as the solvent in steps a) and/or b), and/or c).

4. A process according to claim 1, wherein the free 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid is used as the starting material in step a) and the reaction is conducted in the presence of a base.
- 30

5. A process according to claim 4 wherein a tertiary amine is used in step a) as a base.
6. A process according to Claim 5, wherein the tertiary amine is selected from triethylamine, diisopropylethylamine, ethylpiperidine.
- 5 7. A process according to claim 1, wherein R is 2-piperidyl to obtain Flecainide (I).
8. A process according to claim 7 further comprising the conversion of the Flecainide product to its acetate in step c) of claim 1.
9. Cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid
- 10 of the formula (II) in claim 1.
10. A process for the preparation of the cyanomethyl ester of the formula (II) in claim 1, which comprises reacting 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid or a salt thereof, with a haloacetonitrile of the formula XCH_2CN wherein X is as defined in claim 1 and, if necessary, in
- 15 the presence of an inorganic or organic base.
11. A process according to claim 10, carried out in a suitable inert solvent.
12. A process according to claim 10, wherein 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid is prepared by contacting a halobenzoic acid of the
- 20 formula (III):



- 25 or a salt thereof, wherein X^1 is selected from Br or I, and X^2 is selected from Cl, Br or I, or one of X^1 and X^2 may also be CF_3CH_2O- , with 2,2,2-trifluoroethanol in the presence of a strong base and copper iodide
- 30 and/or copper bromide, in an aprotic solvent.

13. A process for the preparation of Flecainide (I) or a pharmaceutically acceptable salt thereof, substantially as herein described, with reference to the Examples.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 98/00315

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/40 C07D211/26 C07C255/14 C07B43/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Jnal Application No

PCT/IL 98/00315

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